UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/604,945	08/27/2003	Itzhak Bentwich	050992.0300.05USCP	1944

37808 7590 05/13/2008

ROSETTA-GENOMICS
c/o PSWS
700 W. 47TH STREET
SUITE 1000
KANSAS CITY, MO 64112

EXAMINER	
ANGELL, JON E	

ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
05/13/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/604,945	BENTWICH, ITZHAK	
	Examiner	Art Unit	
	J. E. Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-23,33-35 and 45-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-23,33-35 and 45-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/25/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Action is in response to the communication filed on 1/25/08.

The amendment filed 1/25/08 is acknowledged and has been entered.

Claims 21-23, 33-35 and 45-47 are currently pending in the application and are addressed herein.

1. Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Information Disclosure Statement

2. The information disclosure statement (IDS) submitted on 1/25/08 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Claim Rejections - 35 USC §§ 101 and 112

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 21-23, 33-35, 45-47 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or, alternatively, a well established utility, essentially for reasons previously, e.g., see the 12/8/2006 Office Action.

In their broadest embodiments, the claims are drawn to isolated nucleic acid sequences which include the SEQ ID No. 2194, SEQ ID NO: 5264, or complements thereof.

A review of the specification, which is over 28000 pages long, finds general assertions and statements that the present invention relates to a group of bioinformatically detectable novel genes, which Applicant refers to as "genomic address messenger" or "GAM" genes, which are believed to be related to the micro RNA (miRNA) group of genes.

The specification teaches that Micro RNAs (miRNAs), are short ~22nt non-coding regulatory RNA oligonucleotides, found in a wide range of species, believed to function as specific gene translation repressors, sometimes involved in cell-differentiation.

The specification makes general statements that the bioinformatically detectable sequences, GAMs, and the miRNAs they may encode may have utility for regulating target genes and possibly for treating disease.

However, the specification provides no direct or indirect evidence for any specific, substantial, or credible utility of the instantly claimed RNAs encoded by SEQ ID NO:2194 (or complement thereof). There is no disclosure indicating or suggesting that SEQ ID NO:2194 has itself ever been isolated or examined in any way, nor any evidence that the claimed RNA has, in fact, been isolated or prepared or studied or examined under any conditions. Any asserted utility for the claimed sequences appears to be merely speculation based on “bioinformatics,” homology, and secondary structure predictions suggesting that the encoded RNAs are miRNAs because they have a miRNA-like hairpin structure and some degree of sequence homology to some unidentified target sequence. On this basis, and since other miRNAs are known to have gene expression modulating properties, Applicant appears to be asserting that the

bioinformatically detectable sequences, or GAMs, such as the RNAs encoded by SEQ ID NO:2194 also have utility.

However, that utility has not been clearly defined, nor does the prior art search of SEQ ID NO:2194 provide any substantial evidence to show that the RNAs of the size now claimed have any substantial, specific, or credible utility.

Applicant has not shown, and there is no evidence in the prior art to suggest, that the nucleic acids now claimed are expressed in any cell whatsoever. Indeed, the asserted utility and target gene of this and thousands of other miRNA-like sequences appears to be based purely on bioinformatic methods for predicting RNA folding and potential gene targets.

Krutzfeldt et al. (previously presented) state that, in general, the basis for these types of prediction programs is the degree of sequence complementarity between a miRNA and a target UTR, including the presence of a consecutive string of base pairs at the 5′ end of the miRNA known as a 'seed' or 'nucleus', and the cross-species conservation of this binding site. On average, 200 genes are predicted to be regulated by a single miRNA. The authors further state that reviewing the data provided by these algorithms determining candidate targets uncovers the entire gamut of gene categories, such as transcription factors, protein kinases, vesicular trafficking molecules and membrane receptors, suggesting that there is no apparent bias towards one particular function.

Accordingly, while the ability to predict hairpin-like structures and potential gene targets from genomic sequence information appears to be within the state of the art, Krutzfeldt et al. teach that validating the true biological function of any predicted miRNA sequence requires

analyzing miRNA expression patterns, as well as testing the effects of miRNA overexpression and underexpression under different conditions in living cells *in vitro* and *in vivo*.

Thus, while these methods, too, are within the level of skill in the art, Applicant has presented no evidence that any of these validation techniques have, in fact, been carried out with regard to the instantly claimed sequences. That is, no evidence can be found verifying or even suggesting that the sequences encompassed by the claims, including SEQ ID NO:2194, etc., actually gives rise to miRNAs in any cell or organism, and if it does, Applicant has not described or shown any specific, substantial, or credible utility for the expressed miRNA. The fact that an miRNA can regulate gene expression is not specific or substantial because 1) this activity is inherent to almost any miRNA, and 2) because Applicant has not taught any use or purpose for the inhibitory activity nor proposed any specific utility for the asserted down regulation of the target gene of the RNA now claimed.

For instance, Applicant has not provided evidence that the nucleic acid sequences encompassed by the claims play any role in disease. It appears that SEQ ID NO: 2194 may be part of the HIV genome, but there is no indication that SEQ ID NO: 2194 is actually processed in to a miRNA, and if it is, what function the miRNA would have when it is expressed. Accordingly, there is no evidence to suggest that the miRNAs nucleic acid sequences of the instant invention would provide any real world information for a specific use other than general knowledge as to understanding the biological function of the miRNA. Therefore, the information of record amounts to only a starting point and further experimentation would be required in order to identify the function of SEQ ID NO: 2194 and any miRNAs derived therefrom.

The specification generally asserts that a utility of the novel oligonucleotides of the present invention is detection of GAM oligonucleotides and of GR (Genomic Record) polynucleotides—that diagnosis of expression of oligonucleotides of the present invention may be useful for research purposes, in order to further understand the connection between the novel oligonucleotides of the present invention and disease and disease diagnosis and prevention purposes, and for monitoring disease progress.

However, none of these asserted uses meet the three-pronged requirement of 35 U.S.C. § 101 regarding utility, namely, that the asserted utility be credible, specific AND substantial.

This asserted utility is neither specific nor substantial. Since the same can be done with any polynucleotide, the asserted utility is not specific. Also, because the specification does not disclose any specific function for SEQ ID NO:2194, aside from indicating that it may encode an miRNA, it is unclear how or why one of skill in the art would use the information obtained by measuring SEQ ID NO:2194 or its DNA complements or expressed RNAs for any particular purpose aside from general research. Therefore, the asserted utility is not substantial since the application provides no teaching regarding how to use the sequences or expression data for any practical purpose beyond the art-recognized methods of gene expression analysis.

Accordingly, polynucleotide probes derived from the instant invention are simply research intermediates that may help scientists isolate the gene and conduct further experimentation. Such probes can only be used to detect or amplify the genetic material having the same structure as the probes themselves. The probes, vectors and gene expression inhibition systems would provide no immediate, real-world information about the overall structure or function of the underlying gene, for example, aside from its expression patterns.

Neither the instant specification nor the prior art presents any evidence that instant SEQ ID NO:2194, much less the claimed RNA equivalents or complements thereof have any specific biological function. No convincing evidence is found teaching any specific biological function for SEQ ID NO:2194 at all. In fact, no evidence is found suggesting or stating that the RNAs encoded by SEQ ID NO:2194 have been made, isolated, cloned, detected, expressed, or even analyzed in any living cell *in vitro* or *in vivo*.

In summary, no biological or biochemical function has been assigned to the claimed sequences, apart from the general assertions that it, like the thousands of other sequences described in the sequence listing, may correspond to a miRNA and have some direct or indirect relation to human biology and/or cell function.

Thus, the proposed utility of the sequences as therapeutic targets or agents, research tools, material resources for preparing diagnostic probes, vectors, and systems, are simply starting points for further research and investigation into potential practical uses of the claimed nucleic acid sequences.

Brenner v. Manson, 148 U.S.P.Q. 689 (U.S. 1966)

> The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility. Unless and until a process is refined and developed to this point—where specific benefit exists in currently available form—there is insufficient justification for permitting an applicant to engross what may prove to be a broad field.
>
> …a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.

Thus, the specification does not teach a specific and substantial utility for claimed sequences. No evidence has been presented showing or suggesting that any small RNAs derived

from SEQ ID NO:2194 is present in any cell, and, if so, what function these sequences perform. Accordingly, a credible, specific, and substantial nexus has not been established.

Claims 21-23, 33-35, 45-47 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or, alternatively, a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Response to Arguments

Applicant's arguments and the Declaration under 37 C.F.R. 1.132 filed 1/25/2008 have been fully considered but they are not persuasive.

The Office has presented evidence suggesting there would have been reason at the time of filing to doubt the objective truth of the asserted utility. Further evidence is presented herein.

In brief, the application currently claims preprocessed and/or processed miRNA sequences corresponding to SEQ ID NO: 2194 and 5264, respectively. The claimed sequences corresponds to HIV sequences. The sequences and putative gene target were identified bioinformatically. Specific and substantial utility is thereby asserted based on bioinformatic data. The asserted utility has not been experimentally verified. Indeed, there is no experimental evidence of even a single biological function.

1. The Declaration under 37 CFR 1.132 filed 1/25/08 is insufficient to overcome the rejection of claims in view of the totality of the evidence in the pre- and post-filing art. Though made by a proclaimed expert in the art, and containing sound

scientific reasoning, the Declaration represents nothing more than an opinion. While the declaration quantifies the effectiveness of other miRNA prediction algorithms, the declaration does not directly quantify the accuracy and/or false positive/false negative rate of the Inventor's algorithm, the program in question. Instead, the Declaration attempts to show the veracity of the instant prediction software by comparison to related prediction programs. Though unclear from the declaration, the assertion appears to be the instant algorithm is at least as effective as prior art algorithms. However, post-filing art (cited below) indicates it is difficult if not impossible to compare different algorithms without comparing their output using a common dataset, which does not appear to have been done here. The Declaration provides no experimental evidence validating either the predictive quality of the instant algorithm or the utility of the instantly claimed sequences. Such evidence if collected in a statistically relevant manner would be indicative of the accuracy of the algorithm.

2. The Declaration fails to address the hundreds if not thousands of sequences embraced by the instant claims sharing at least 77.3% identity to SEQ ID NO: 5264. Neither the disclosure nor the literature provide any reason to believe sequences less than 100% identical to the instant sequences will inhibit the target HIV gene, and the Declaration fails to address or explain why sequences having less than 100% identity to the bioinformaticlly identified sequences would nevertheless inhibit the target HIV gene.

3. The question remains whether the bioinformatically predicted miRNAs now claimed would, more likely than not, have the utility asserted. The answer lies in the predictive quality of the program used to identify the miRNAs and their target sites. A quantifiable value is not readily apparent to the Examiner from the facts of record. Indeed, the Examiner is unable to find any disclosure by the inventor either in the instant application or in the pre- or post-filing art clearly articulating the sensitivity or false positive rate of the instant algorithm. A simple statement supported by actual experimental evidence, showing the algorithm correctly predicts an miRNA and its activity more than half of the time and has an acceptable false positive rate would be sufficient to overcome the instant rejection. Currently, however, neither the Declaration nor the specification addresses this question directly.
4. Comparative algorithms used in the art are said to have false positive rates of between 22% and 39%. See Bentwich et al. (2005) *FEBS Lett.* 579:5904-5910, page 5907; and the Declaration, Point 4. See also Martin et al. (2007) *J. Biosci.* 32:1049-1052 at page 1049, 4th full paragraph.
5. Martin et al. (2007) *J. Biosci.* 32:1049-1052, reviewing the state of the art of miRNA prediction programs, state mammalian miRNA targets are considered difficult to predict because miRNA targets display only partial complementarity to the mature miRNA sequence (pg. 1049). Martin et al. further state that "Given the high level of both false-positives and false-negatives resulting from the application of current miRNA target prediction programs, it is clear that

experimental testing of predicted miRNA targets is critically important in order to validate/confirm any putative miRNA-target gene combination" (pg. 1050, 4th complete paragraph). Martin et al. further teach that miRNA prediction programs rely on sequence, structure, and evolutionary conservation information to predict genes likely to be targeted by miRNAs, but that the requirement for conserved sites means that non-conserved sites, which may represent real targets, are completely missed.

6. The post-filing art suggests that it is difficult to estimate the true false positive/negative rates of miRNA prediction programs because few validated miRNA targets are known. See Maziere et al. (2007) *Drug Discovery Today* 12:452-458, page 457. Maziere et al. in their article entitled "Prediction of miRNA Targets," further state that comparison of miRNA prediction efficiencies among different programs is not currently possible because many of the programs are not available for download and use on a common dataset; thus, Maziere et al. cast doubt on the reliability of the statements made in the Declaration, comparing similar programs to that used by the Inventor. Again, no evidence has been presented by Declarant directly comparing the output of the instant algorithm with the other cited programs when presented with a common dataset.
7. Smalheiser et al. (2006) *Methods Mol. Biol.* 342:115-127 in an article entitled "Complications in miRNA Target Prediction" state that complementarity between miRNAs and their targets is not the only factor that may govern which miRNA-mRNA target interactions are effective in vivo. One must consider the potential

importance of mRNA target secondary structure, as well as the strong possibility that RNA-binding proteins may participate in miRNA recognition. Furthermore, both miRNA and mRNA need to be coexpressed in proper amounts within the cell for effective interaction to occur, and A-to-I editing of RNA might abrogate potential mRNA targets from being effectively silenced by the RNA-induced silencing complex (page 124). Smalheiser et al. further teach that not all mammalian miRNAs interact with their targets via "short seeds," complementary regions of 6-8 nucleotides, but, instead, may interact via "long" seeds and perfect matches (page 115-6), and because new miRNAs are constantly being discovered this list of binding determinants may not be complete.

8. A search of putative target sites of the claimed miRNA, SEQ ID NO:5264 and 2194, using the miRanda program available at www.microrna.org, finds thousands of putative target sites in thousands of genes.
9. Thus, multiple factors are involved in miRNA-target binding and recognition.
10. Thus, in view of the totality of the evidence, one of skill would have reason to doubt the objective truth of the asserted utility. While the instant algorithm provides a list of putative miRNAs and corresponding target sites, there is reason to question whether the bioinformatic algorithm used to produce this list correctly identifies an miRNA and its function (i.e., at least one biological function) with minimally acceptable false positive and false negative rates such that one of skill would believe the miRNA would, more likely than not, inhibit the gene predicted by the software. Without experimental validation or any verifiable evidence of the

accuracy and error rates of the instant program, and in view of the state of the art at the time of invention, one of skill would reasonably question the certainty of the prediction at the time of filing.

11. The skilled artisan would be led to believe only that the instantly claimed nucleic acids require further research to verify the asserted utility.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. E. Angell whose telephone number is 571-272-0756. The examiner can normally be reached on Monday-Thursday 8:00 a.m.-6:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Douglas Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/J. E. Angell/
Primary Examiner, Art Unit 1635

/J. E. Angell/
Primary Examiner
Art Unit 1635